POSTER SESSION 1

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The microRNA-221/222 family is differentially regulated in cardiac disease and counteracts pressure overload-induced cardiac remodeling in mice

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Purpose: Despite major advances in the treatment of cardiovascular diseases, heart failure (HF) remains one of the top causes of death world-wide. The implications of microRNAs in this process are well accepted but still only incompletely understood. The microRNAs 221-3p and 222-3p are processed from a common precursor and share the same seed sequence and thus form the microRNA-221/222 family (miR-221/222). Both microRNAs were found to be involved in myoblast differentiation and are upregulated after aortic banding in mice. We therefore hypothesized that the miR-221/222 family is involved in the pathophysiology of cardiac hypertrophy and failure upon pressure overload.

Methods and results: In a genome wide screen for microRNAs regulated in human dilated cardiomyopathy, we found miR-222 levels to be significantly decreased (p < 0.01). MiR-221/222 were also downregulated in neonatal rat cardiomyocytes (nRCMs) upon stimulation with the pro-hypertrophic compound phenylephrine (PE) (p < 0.05). Interestingly, the overexpression of these miRs in nRCMs using mimics significantly blunted the induction of the hypertrophy markers Bnp and skeletal alpha actin (Acta1) in nRCMs upon stimulation with PE.

To investigate the role of miR-221/222 in pressure overload-induced heart failure, we simultaneously injected anti-miR-221 and anti-miR-222 antisense oligonucleotides (ASOs) or scrambled control oligonucleotides (SCOs) in male C57BL/6 mice 3 days before implanting angiotensin II-filled osmotic minipumps (AngII, 2.5 mg/(kg d)). After 4 weeks, we assessed cardiac function and histology as well as molecular changes in the left ventricle. Surprisingly, we did not find an effect of miR-221/222 inhibition on overall cardiac hypertrophy after AngII infusion (HW/TL: 8.04 vs 7.92 mg/mm, p > 0.05). However, interstitial fibrosis was significantly increased upon AngII stimulation in mice that received miR-221/222 ASOs as compared to SCOs (6.1 vs 3.7% LV area, p < 0.05). On the mRNA level, these mice also showed a 2.9-fold higher induction of Anp upon AngII stimulation (p<0.10), in line with anti-hypertrophic effects of miR-221/222 mimics shown in vitro.

Conclusions: Taken together, our results indicate a protective effect of the microRNA-221/222 family in the stressed heart. Inhibition of miR-221/222 prior to pressure overload in mice led to increased fibrosis indicating adverse remodeling. In vitro, a direct effect of miR-221/222 overexpression on the hypertrophic response of nRCMs could be shown. Further experiments will aim at identifying the function of the miR-221/222 family both in cardiac fibroblast and cardiomyocytes.